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# Enhancement of Synaptic Efficacy by Presynaptic $GABA_B$ Receptors

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## Summary

**Activation of presynaptic inhibitory receptors or high-frequency synaptic stimulation normally inhibits excitatory synaptic transmission by reducing transmitter release. We have explored the interactions between these two pathways for reducing synaptic strength and found that for synapses stimulated at high rates, agonists of the $GABA_B$ receptor become excitatory and strengthen transmission. At an auditory glutamatergic synapse featuring strong synaptic depression, the $GABA_B$ agonist baclofen reduced by 90% postsynaptic currents elicited at low frequency. By contrast, synaptic currents elicited at high frequencies were 5-fold larger in baclofen and had a markedly increased likelihood of firing well-timed postsynaptic action potentials. Presynaptic $GABA_B$ receptors may thus regulate transmitter release to enable sustained transmission at higher stimulus frequencies, thereby extending the dynamic range of neural circuits.**

## Introduction

Short-term synaptic depression is an activity-dependent reduction in synaptic strength characteristic of a wide variety of synapses (Takeuchi, 1958; Elmquist and Quastel, 1965; Furukawa and Matsuura, 1978; Zucker, 1989; Zhang and Trussell, 1994a; Dobrunz and Stevens, 1997). Possible mechanisms for depression include vesicle depletion (Elmquist and Quastel, 1965), presynaptic autoreceptor activation (Barnes-Davies and Forsythe, 1995; von Gersdorff et al., 1997), or postsynaptic receptor desensitization (Otis et al., 1996a). In general, synapses that have a high probability of transmitter release are subject to depression, particularly when the density of release sites ensures a high concentration of transmitter (Zucker, 1989; Otis et al., 1996a).

Recent studies have suggested that depression "equalizes" the strength of cortical synapses with different initial release probabilities (Markram and Tsodyks, 1996; Abbott et al., 1997). However, the role of depression in information transfer is not well understood, in part because synapses in vitro are usually activated below physiological rates. Moreover, the significance of depression would be expected to vary throughout the nervous system, depending on the nature of the neural signals that are being encoded at any given synapse. At the end-bulb glutamatergic synapse made by auditory nerve fibers on neurons of the nucleus magnocellularis (nMAG), repetitive synaptic activity results in marked depression (Trussell et al., 1993) that may reduce synaptic potentials below threshold (Zhang and Trussell, 1994b). Factors that control the onset of depression are therefore of clear significance to the function of these neurons in relaying auditory signals.

We have explored whether or not the action of presynaptic GABA receptors may regulate the onset of depression observed during repetitive stimulation of the eighth, auditory nerve. nMAG neurons and their postsynaptic target cells in the nucleus laminaris receive GABAergic innervation from the superior olive, which is, in turn, activated by fibers from the cochlear nucleus angularis (Lachica et al., 1994). Pena et al. (1996) have suggested that inhibition by $GABA_A$ receptors in nucleus laminaris enhances binaural coincidence detection during exposure to high-intensity sound. However, high-intensity sounds would be expected to induce high rates of eighth nerve firing and so lead to marked synaptic depression. A mechanism for relief of depression would therefore serve to sustain auditory signal processing upon increase in sound intensity. We have focused on actions of presynaptic $GABA_B$ receptors. The $GABA_B$ receptor agonists GABA and baclofen inhibit the size of excitatory postsynaptic currents (EPSCs) in nMAG by reducing the level of transmitter release (Otis and Trussell, 1996). We find that the effect of reducing release probability in auditory neurons is strikingly different than that predicted from the cortical studies described above. With low-frequency stimulation ($\leq$100 Hz), similar to rates measured in vivo in the absence of acoustic stimuli (Manley et al., 1985, 1997; Warchol and Dallos, 1990), depression is minimal, and baclofen always makes synapses weaker than control. Remarkably, at the high neural firing rates characteristic of acoustic stimuli in vivo (200–500 Hz; Sachs and Abbas, 1974; Liberman, 1978; Manley et al., 1985, 1997), baclofen delays the onset of depression and strongly enhances the ability of synapses to drive their postsynaptic cells to action potential threshold.

## Results

### Depression of EPSCs

Voltage-clamp studies were conducted in order to document the degree of depression of the synaptic current at different stimulus rates and its modulation by activation of $GABA_B$ receptors. In brain slice preparations, activation of single auditory nerve fibers produced large inward EPSCs in nMAG neurons voltage clamped to −30 mV. As shown in Figure 1, repetitive stimulation of the synapse resulted in progressive decline in the EPSC amplitude to a stable level that was dependent on the rate of firing. For example, after ten shocks at 50 Hz, EPSCs recorded at 36°C depressed to a level that was 50% of the first EPSC in the train, whereas at 333 Hz, the tenth EPSC depressed to less than 3% of the first EPSC (Figures 1A and 1C). These data are summarized in Figure 1D. Depression increased sharply with reduction of temperature, as shown in Figures 2A and 2B, in

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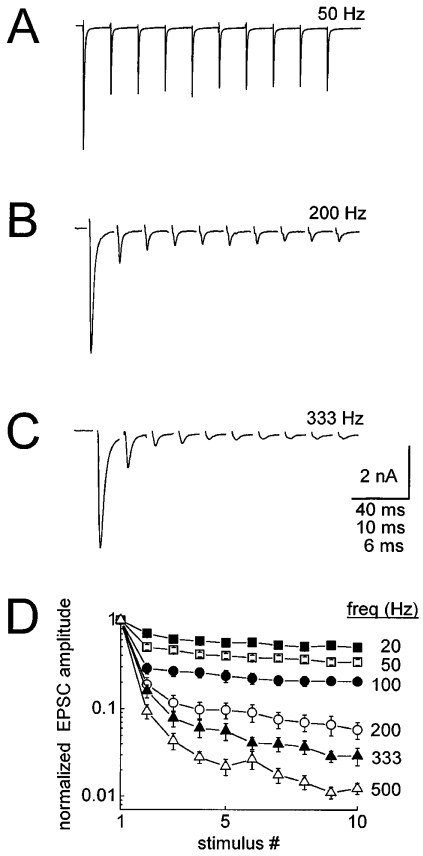


Figure 1. Control of Synaptic Strength by Stimulus Rate

(A–C) Average of five to ten trains of EPSCs recorded at 36°C, elicited at 50, 200, and 333 Hz and delivered at 30 s intervals. Note different time axis on calibration bar.

(D) EPSC amplitudes normalized to the first EPSC in a train at each frequency and plotted against stimulus number in the train. Data pooled from seven neurons, with frequencies as indicated.

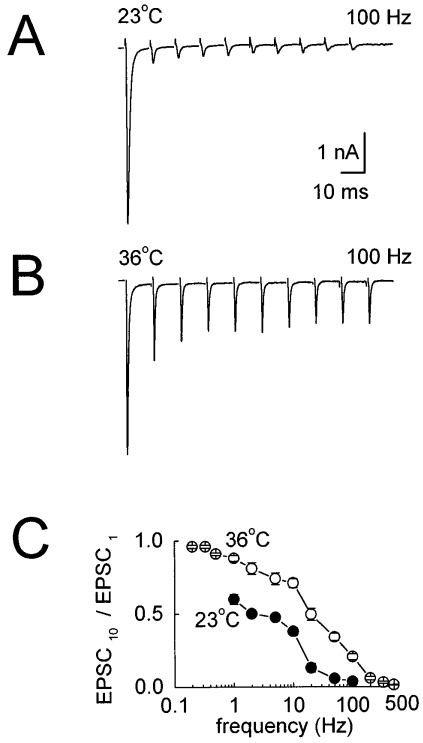


Figure 2. Temperature and Frequency Dependence of Depression

(A and B) Average of ten trains of EPSCs recorded at 100 Hz at 23°C and 36°C. Data from two different neurons.

(C) Relative depression after ten stimuli plotted against stimulus frequency for cells at 23°C (five to 19 cells per point) and 36°C (seven cells per point).

which depression of EPSCs at 50 Hz is ten times greater at room temperature than at 36°C. The relation between stimulus rate and the extent of depression at both temperatures is shown in Figure 2C. Such a relation would be expected if each EPSC results in depletion of vesicles or desensitization; in this case, the final level of depression would reflect an equilibrium between the ongoing stimulus frequency and the rate of recovery following each stimulus (Elmquist and Quastel, 1965; Zucker, 1989). The reduction in depression at warmer temperatures may therefore reflect an accelerated rate of recovery between stimuli, perhaps related to the turnover rate of vesicle pools and/or clearance rate of desensitizing transmitter from the synaptic cleft.

Application of baclofen (100 μM) reduced the amplitude of single EPSCs 89% ± 2% (n = 23) and, with paired stimuli, converted depression to slight facilitation (Figure 3A), as noted previously (Otis and Trussell, 1996). This effect of baclofen can be interpreted entirely in terms of a decrease of transmitter release, as (1) decrease of release by a low calcium–high magnesium extracellular solution (see Experimental Procedures) produced a parallel reduction both in EPSC amplitude and depression (Figures 3A and 3B), and (2) postsynaptic $K^+$ currents that may be activated by $GABA_B$ receptors were blocked with intracellular cesium, consistent with the absence of a change in postsynaptic holding current upon application of baclofen.

Since increasing stimulus frequency and reducing release probability apparently have opposing effects on the relative amount of depression, we next compared the *absolute amplitude* of EPSCs elicited at different stimulus rates, with and without baclofen. Figure 4Ai shows a train of ten EPSCs delivered at 200 Hz in control and baclofen solutions. In Figure 4Aii, these traces are overlaid and illustrate that whereas the initial baclofen EPSC is reduced about 90% relative to control, for all subsequent stimuli, the control EPSCs (horizontal arrows) were actually smaller than EPSCs in baclofen. In contrast, when the stimulus frequency was lowered to 50 Hz, EPSCs in baclofen remained smaller than control throughout the train, as shown in Figures 4Bi and 4Bii. Thus, baclofen was only absolutely inhibitory for the initial EPSC or during low-frequency stimuli. At higher stimulus rates, EPSCs were larger in the presence of baclofen. This conclusion is further supported by the analysis in Figure 4C, which shows the ratio of EPSC amplitudes in baclofen and control at different points in trains of responses. Below 100 Hz, EPSCs in baclofen were always smaller than control, whereas at 200 Hz and above, EPSCs in baclofen after the first two to three

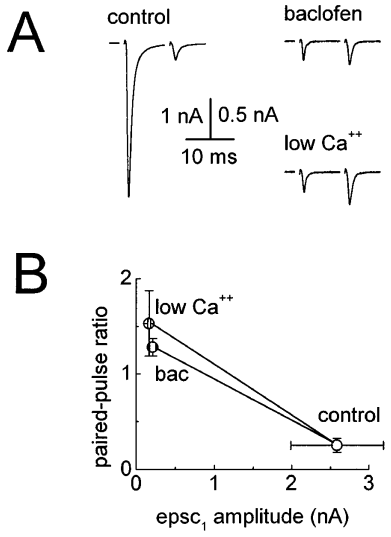


Figure 3. Activation of $GABA_B$ Receptors Inhibits Transmitter Release

(A) Comparable inhibition of EPSC amplitude and depression by 100 μM baclofen and by reduction of bath calcium (0.5 mM $Ca^{2+}$/3 mM $Mg^{2+}$). Data from one neuron at 23°C.

(B) Average effect of baclofen (100 μM) and low bath $Ca^{2+}$ on EPSC amplitude and paired-pulse depression ($EPSC_2/EPSC_1$) at 23°C (three cells).

stimuli were always larger than controls, with a maximal relative enhancement of 567% ± 52% for the tenth EPSCs at 500 Hz (four cells).

The apparent frequency sensitivity of baclofen's action on the absolute size of the EPSC is shown in Figure 4D, in which the frequency dependence of the amplitude of the EPSC after ten stimuli, normalized to the first EPSC in control solutions, is plotted for control and baclofen-treated cells. The crossing point of the two curves indicates the frequency range at which activation of $GABA_B$ receptors becomes excitatory. Figure 4D indicates that this action of baclofen on the relative amplitude of the EPSCs is due to the fact that control synapses activated at high rates depress enormously, while baclofen renders the synapse relatively insensitive to frequency. Thus, at 23°C or 36°C, the amount of enhancement by baclofen of EPSC amplitude is predictable solely from the amount of depression the synapse shows before application of the drug (Figure 4E).

This action of baclofen presumably reflects a reduction in the probability of transmitter release. In order to test this hypothesis, bath calcium was again reduced and bath magnesium elevated (see Experimental Procedures) to reduce release probability. This manipulation lowered the amplitude of low-frequency EPSCs at 36°C by 86% ± 4% (n = 4 cells), similar to the average reduction observed with baclofen. For these cells activated at 200 Hz, the ratio of the amplitude of the tenth EPSC in low calcium to that in control solution was 3.3 ± 0.7, as compared to 2.2 ± 0.3 for the baclofen/control ratio (n = 7; see Figure 4C). Taken together, these data indicate that reduction in the probability of release reduces the likelihood of depletion of transmitter or desensitization of postsynaptic receptors and so enhances synaptic strength.

### Control of Safety Factor

The results described above imply that the initial reduction of release by presynaptic $GABA_B$ receptors could ultimately improve transmission of signals through synapses firing at high rates. To test this hypothesis, recordings were made under current-clamp conditions (Zhang and Trussell, 1994b) at 36°C to monitor excitatory postsynaptic potentials (EPSPs) and action potential activity during synaptic stimuli. As shown in Figure 5A, single EPSPs reached threshold within 0.5 ms and showed a slow decay phase, the latter reflecting the delayed clearance of transmitter at the end-bulb synapse (Zhang and Trussell, 1994b; Otis et al., 1996b). In 10 μM baclofen, EPSPs were still suprathreshold but because of their reduced size, reached threshold with a slightly greater delay and no longer showed a slow phase of decay (Figures 5Aii and 5Aiii). The persistence of suprathreshold EPSPs in the presence of baclofen at concentrations that reduced the EPSC by nearly 90% indicates the very high safety factor of the nMAG synapse. In response to stimuli at 333 Hz, control EPSPs depressed to subthreshold levels within a few stimuli (asterisks in Figure 5B). In baclofen, by contrast, suprathreshold EPSPs were apparent even late in a train of 15 responses. At lower stimulus rates, however, all EPSPs were suprathreshold with or without baclofen, as shown in Figure 5C. Figure 5D summarizes the effect of baclofen on the probability of firing action potentials during trains delivered at different rates, showing that baclofen increased the ability of the synapse to sustain suprathreshold activity with increase in stimulus rate but had little effect on spike probability at lower rates. Thus, activation of $GABA_B$ receptors extended the effective range of transmission to rates that would under control conditions rapidly shut off the relay of presynaptic signals.

### Field Potential Recordings

This conclusion was confirmed by making extracellular field potential recordings from nMAG during activation of auditory nerve fibers in a whole brainstem preparation maintained in vitro (Jackson et al., 1985). In this recording configuration, the voltage deflection marked AV in Figure 6A corresponds to the presynaptic compound action potential volley, and the second large deflection marked P2 reflects the compound action potential from postsynaptic nMAG axons (Jackson et al., 1985). By monitoring pre- and postsynaptic field potentials, we were able to easily assess the average effect of repetitive stimulation on action potential generation and to control for presynaptic effects of baclofen on the action potential waveform. Synaptic depression was evident as a reduction in the amplitude of P2, with no change in AV during a train of stimuli, as shown in Figure 6A, and corresponds to a reduction in the fraction of postsynaptic cells that respond to eighth nerve stimulation with action potentials. At 38°C–41°C, near avian body temperature, little P2 depression was apparent at 100 Hz (data not shown) but was clearly evident during trains of 28 shocks at 333 Hz (Figure 6A). As shown in Figure 6B, baclofen had only a small effect on the initial fraction of subthreshold fibers and no effect on AV (thick line)

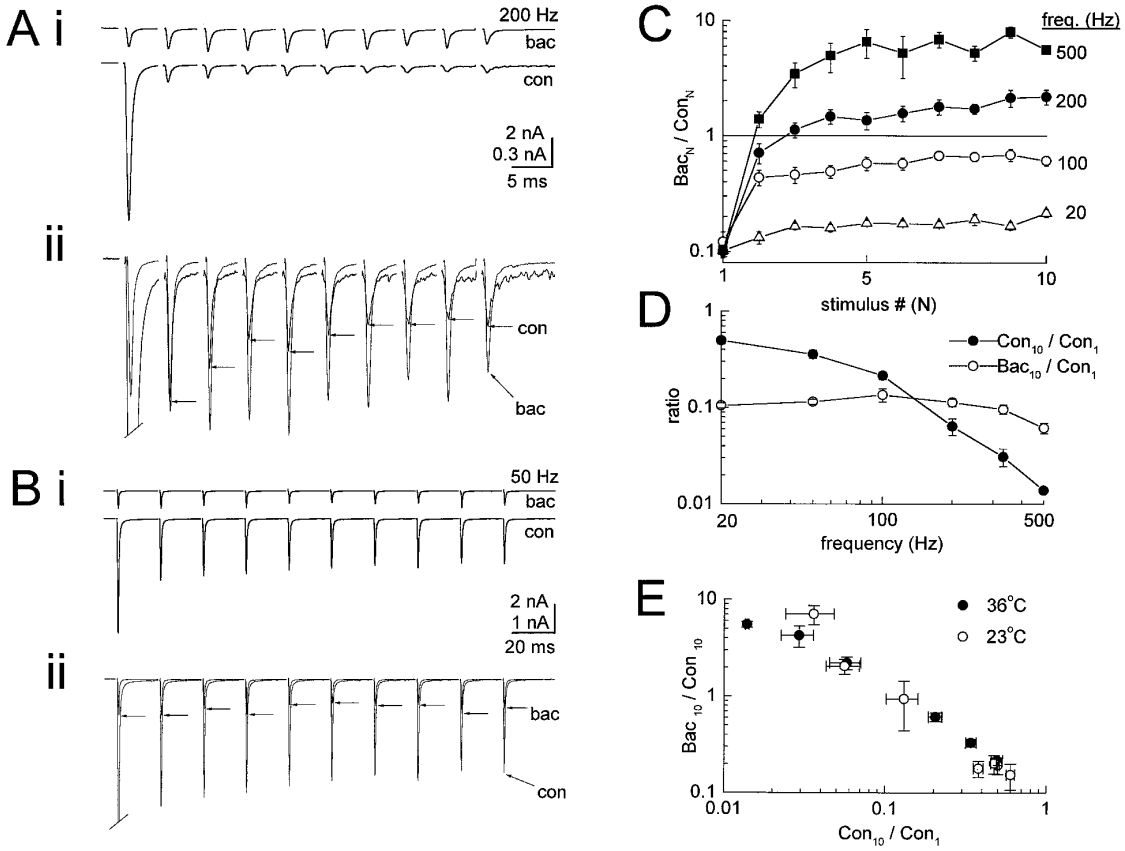


Figure 4. Baclofen Enhancement of Synaptic Strength during High Frequency Stimuli

(Ai) Average of ten trains of 200 Hz stimuli delivered at 30 s intervals in the presence (bac) or absence (con) of 100 μM baclofen. In (Aii), these records are superimposed to illustrate that late in the train, control EPSCs (horizontal arrows) are smaller than those recorded in baclofen. (Bi and Bii) In the same cell, lower frequency stimuli show the opposite effect, such that EPSCs in baclofen are smaller than control.

(C) Ratio of EPSC in baclofen to that in control solution at each point in a train of n = 10 stimuli at indicated frequency. Mean of four to seven cells.

(D) EPSC amplitudes at the end of a ten stimulus train for control and baclofen treatments, normalized to the initial control peak ($Con_{10}/Con_1$ and $Bac_{10}/Con_1$, respectively), plotted against frequency. The intersection of the plots between 100 and 200 Hz shows the frequency at which baclofen produces a net enhancement of EPSC amplitude. Data in (A)–(D) obtained at 36°C.

(E) Relative amplitude of tenth EPSC in baclofen, plotted against the degree of depression shown in control solutions at the indicated temperatures. This relationship indicates that the apparent enhancement of EPSC size in baclofen is dependent on the extent of depression in control solutions.

but significantly delayed depression of P2 late in the train (closed circles), relative to control (open circles). Less depression overall is seen in the brainstem than in brain slices because in the latter, only one of two to three eighth nerve terminals per nMAG cell is being stimulated (Zhang and Trussell, 1994b).

Examination of the relative timing of the P2 population spike gave additional insight into the role of $GABA_B$ receptors during trains of synaptic stimuli. In Figure 6A, it is apparent that during a train, the peak of the population spike is progressively delayed. This delay in the timing of the spikes is reduced in baclofen, as expected, since larger EPSPs would reach spike threshold more quickly. Figure 6C summarizes the effect on changes in spike timing during trains and shows that activation of $GABA_B$ receptors not only helps maintain suprathreshold EPSPs at high frequency but also preserves the timing of action potentials during the train. For example, initial P2s in control solution occur earlier than P2s in baclofen, but by the end of the train, control P2s occurred later than in baclofen. The difference in P2 timing at the end of the train, 70 μs, is similar to the time required for a fully lateralized sound to travel across the head of a small bird. For example, for an animal with an interaural distance of 2.5 cm, a sound would require 83 μs to pass from one ear to the other, traveling at 30 cm/ms.

## Discussion

Our results indicate that presynaptic modulators that reduce excitatory transmitter release cannot be interpreted simply as inhibitory, as their action is dependent on the level of activity of their target synapses. For synapses that are active at very high rates, an initial inhibition of release ultimately results in an enhancement of synaptic strength by preventing synaptic depression. This "context-dependent" action of a modulator has not been previously described because of the narrower range of stimulus rates that are typically employed. The

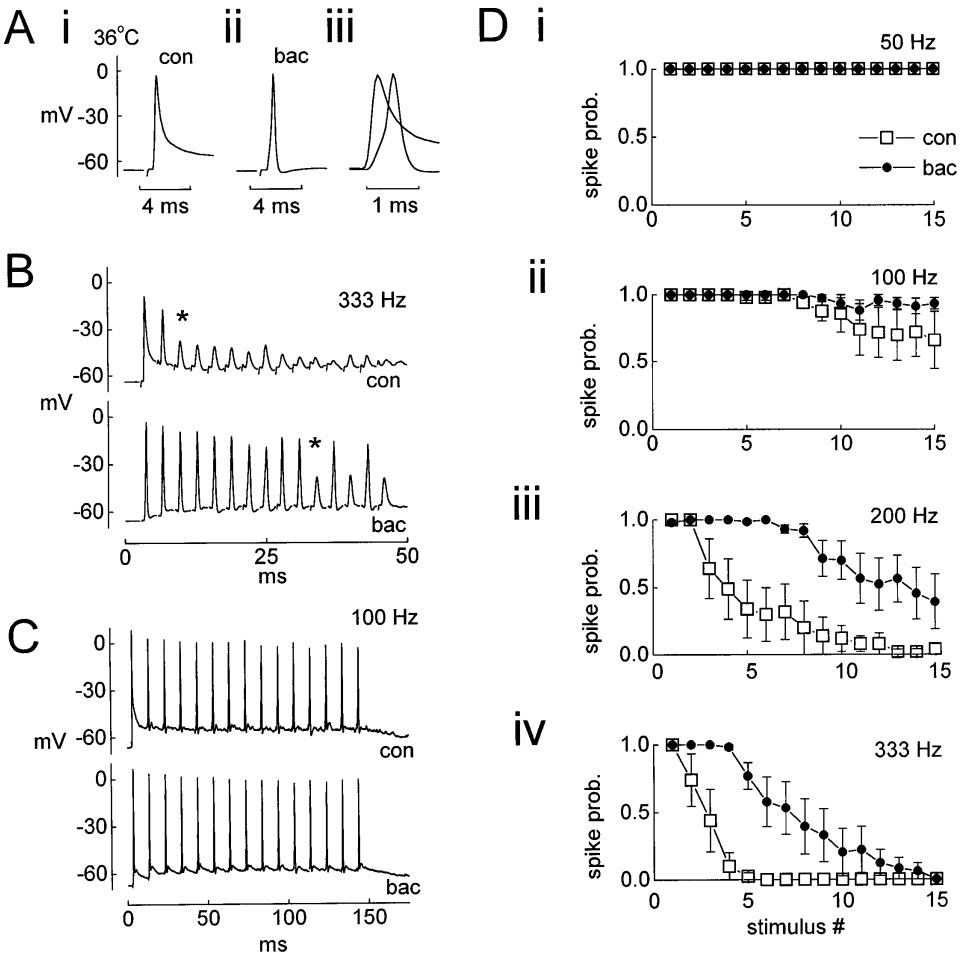


Figure 5. Baclofen Promotes Suprathreshold Transmission at High Frequencies

(A) With single stimuli, 10 μM baclofen (bac) reduces the size of the late phase of the EPSP relative to control (con; see overlay in panel iii) but maintains suprathreshold transmission.

(B) Individual train of 15 stimuli delivered at 333 Hz. In the control trace, EPSPs are subthreshold (asterisks) after only three stimuli, while in baclofen, suprathreshold EPSPs may still be observed at the end of the train.

(C) At 100 Hz in the same cell, EPSPs are suprathreshold throughout the train, with or without baclofen.

(Di–Div) Summarizes the frequency dependence of the probability of firing action potentials (spike probability), measured as the fraction of suprathreshold EPSPs at each point in a train for ten repetitions delivered at 30 s intervals. Included are data for four different frequencies, as indicated, in control (open squares) and baclofen (closed circles).

inhibition of the depression by pharmacological reduction of transmitter release has been described in a wide variety of preparations (Lev-Tov and Pinco, 1992; Barnes-Davies and Forsythe, 1995; Isaacson and Hille, 1996; Varela et al., 1997). Most often, these studies find that repetitive stimulation on the order of 10–20 Hz "equalizes" synaptic strength at strong and weak synapses (Markram and Tsodyks, 1996; Abbott et al., 1997; O'Donovan and Rinzel, 1997). By extending the range of stimulus frequencies to include rates above 100 Hz, we have found that synaptic strength at intensely active synapses is greatest under conditions that inhibit transmitter release.

Classic models of transmission describe release as a product of the number of release sites and their individual release probabilities, $P_R$ (Zucker, 1989; Stevens, 1993). The reason for the enhancement of synaptic strength observed here is most likely that reduction of release probability lowers the extent of vesicle depletion and postsynaptic receptor desensitization following each presynaptic action potential. We suggest that the ability to modulate $P_R$ by presynaptic receptors may represent an adaptation not just to reduce the overall level of release but to titrate the rate of vesicle depletion and receptor desensitization with $P_R$, in order to maintain maximal synaptic strength at different stimulus rates. Synapses most sensitive to such regulation would be those having a high initial $P_R$, as these are more likely to undergo depression. It is important to consider that such would not be the case if presynaptic inhibition occurred by reduction of the number of available release sites, effectively "switching off" individual synapses. In that case, synaptic strength would be reduced equivalently at all frequencies.

In the auditory system, these results may have particular significance. Avian nMAG neurons fire spontaneously

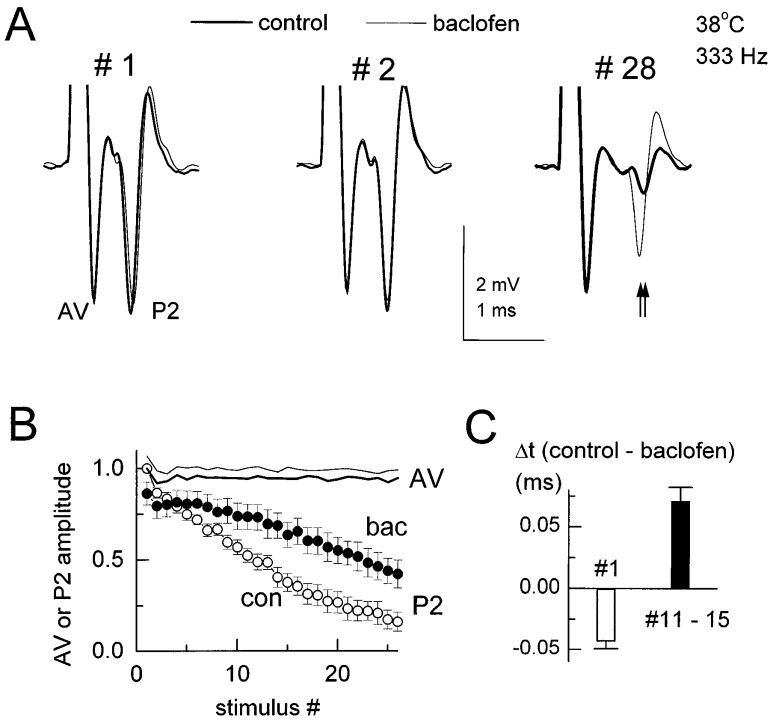


Figure 6. Field Potential Recordings during Stimulus Trains

(A) Field potentials in nMAG recorded at 38°C with (thick line) and without (thin line) 10 μM baclofen. Shown are the first, second, and 28th responses delivered at 333 Hz. Note the decline in control P2 (postsynaptic spike) waveform and shift in latency of P2 with and without baclofen. Double arrows indicate difference between baclofen and control in their P2 latency.

(B) Effect of 10 μM baclofen on depression of P2 and AV waveforms during 333 Hz trains. Data from four brainstems. Shown are measurements of P2 (closed circles, baclofen; open circles, control) and AV (thick line, baclofen; thin line, control). All amplitudes of AV and P2 normalized to those of the first response in control solutions.

(C) Shift in timing of postsynaptic action potentials during trains by baclofen. The latency from onset of stimulus to peak of the P2 wave in baclofen was subtracted from the same latency in controls. This timing difference was then determined for the first response in a train (hatched bar) and also averaged for the 11th through 15th responses (filled bar) in the train (333 Hz, 38°C).

at rates of nearly 100 Hz (Manley et al., 1985, 1997; Warchol and Dallos, 1990); during acoustic stimulation, cochlear nuclear synapses will fire at rates up to several times higher (Sachs and Abbas, 1974; Liberman, 1978; Manley et al., 1985, 1997). In this context, our results suggest that in vivo levels of activity almost certainly result in severe synaptic depression, particularly during presentation of intense sound. nMAG neurons project bilaterally to nucleus laminaris, the coincidence detectors of the so-called auditory timing pathway for localization (Konishi et al., 1988). Reduction of depression may represent a means for extending the range of sound intensities over which synapses in brainstem auditory nuclei can utilize cues for determining the location of sounds in space.

As noted above, neurons in the avian cochlear nuclei receive GABAergic inputs from the superior olive. While avian superior olivary neurons are activated by acoustic stimuli (Lachica et al., 1994), it remains unclear to what sound frequencies or intensities they are most sensitive. If their synapses in nMAG are active during ongoing auditory activity, superior olivary neurons could prevent depression only if they release GABA *prior* to the onset of firing in nMAG. While this seems unlikely to occur for an intense, sustained tone, it may be possible with periodic, natural acoustic stimuli that would allow recovery to occur between stimuli. In this way, a relatively long-lasting inhibition by means of metabotropic GABA receptors could influence the response of nMAG neurons to periodic excitatory stimuli. An additional consequence of the effects described here may arise if presynaptic GABAergic modulation was itself regulated. At the high stimulus rates described here, synapses without $GABA_B$ receptor activation would reliably, but transiently, relay signals. Thus, the presence or absence of GABAergic modulation may determine what aspect of a sensory stimulus is emphasized; modulated synapses would transmit in response to sustained stimuli, while unmodulated synapses may provide information only about the onset of an acoustic stimulus.

## Experimental Procedures

### Brain Slice Recordings

Brain slices (350 μm) were made from 18–19 day embryonic chicks as described previously (Zhang and Trussell, 1994a). During recordings, slices were superfused with an oxygenated saline (in mM: 140 NaCl, 20 glucose, 10 HEPES, 5 KCl, 3 $CaCl_2$, 1 $MgCl_2$) supplemented with 5 μM SR95531, 2 μM strychnine, 100 μM DL-APV, and 5 μM 7-Cl-kynurenate to block $GABA_A$, glycine, and NMDA receptors. In low $Ca^{2+}$ solution, the divalent ion concentrations were changed to 0.5 mM $CaCl_2$ and 3 mM $MgCl_2$. Individual neurons were viewed with DIC optics and patch clamped using an Axopatch 200A amplifier. Series resistance (mean, 5.5 ± 0.4 MΩ, n = 23) was compensated by 80%–90% (mean, 87% ± 1%, n = 23). As discussed in Zhang and Trussell (1994a), the amplitude and time course of EPSCs are accurately measured under these recording conditions. In voltage-clamp experiments, pipettes were filled with (in mM) 70 $Cs_2SO_4$, 85 sucrose, 5 BAPTA, 10 HEPES, 4 NaCl, 1 $MgCl_2$ (pH 7.3). During current-clamp experiments, pipettes contained (in mM) 140 K-gluconate, 5 NaCl, 1 $MgCl_2$, 10 HEPES, 1 EGTA (pH 7.3). Baclofen was applied either by bath application or by pressure ejection directly to the cell body. Individual presynaptic axons were stimulated by 0.10–0.25 ms, 5–30 V isolated voltage pulses delivered through a second patch pipette visually positioned onto nearby myelinated fibers 20–100 μm from the cell body. Currents and potentials were filtered at 10 kHz and digitized at 20 kHz. Means are given ± SE.

### Brain Stem Recordings

Intact brain stems, cut just rostral to the spinal cord and caudal to the tectal commissure, were secured ventral side down in a small dish (1.5 ml volume) and superfused with the same saline as used for slices but with no added blocking agents. The whole auditory nerve stump was stimulated with a suction pipette delivering 80

μs, 12 V pulses. Field potentials were measured with a patch-type pipette filled with 2 M NaCl inserted 20–80 μm into nMAG, which was apparent on the dorsal surface of the brain stem when viewed with a stereomicroscope. Potentials were filtered at 5 kHz and digitized at 50 kHz. The identification of components in the field potential was consistent with that described by Jackson et al. (1985).

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